# LETTERS *to the Editor*

## Cancer Immunotherapy: A Word of Caution About "A Word of Cautious Dissent"

TO THE EDITOR: In a recent critique of the potential therapeutic value of cancer immunotherapy,[1] Dr. Hall sets forth a theoretical basis for limitations. He points out the weakness of human tumor antigens and relates that many human tumor antigens have proven to be products of normal cells which are either in the wrong anatomic location or of fetal origin. This last observation should theoretically lead to a kind of "horror autotoxicus" resulting from effective immunotherapy since tumor cells are not different from some ontogenic phase of their normal counterpart.

Yet extension of these objections provides a rationale which should make immunotherapy successful. Burnet's concept[2] is that the "immune system" resulted from an evolutionary pressure for "immune surveillance" of cancer. It would appear much more likely that "immunity" evolved as part of an ontogenic control mechanism necessary for the development of higher organisms. The "crudely compartmentalized" lower organism can differentiate with chemical gradients and inducing substances. In higher organisms, mesenchymal subcompartments interact with each other and with parenchyma in a physiologically and anatomically intricate way.

In these organisms, there would be evolutionary pressures for mechanisms which detect and repair the loss of integrity of compartmental interfaces during development and during repair of certain types of injury. Evidence for this viewpoint is the rapid removal of non-neoplastic ectopic parenchymal cells, the ontogenically late development of immunity in the "higher" organism, and the ability of organisms to detect antigens which are normally present some time during development.[3,4]

One may view invasive cancer as a breach in parenchyme-mesenchyme or mesenchymal subcompartment relationships. Going beyond a concept that many tumors are "no different from normal," I would propose that they are "less different from normal" than tumor and normal parent are from other tissues. This "less different" state should make tumors especially amenable to "immune controls," as a normal developmental control mechanism already exists for this very purpose.

This concept is in consonance with that of an antitumor effect of non-specific stimulation of "immunity." One simply has to "beef up" a normal developmental control mechanism. Those cancers which are due to true neo-antigens may not have much therapeutic edge on those which are "less different" from their parent tissue and hence recognizable by normal mechanisms.

The fact that clinical immunotherapy has not been a smashing success to date may be due to the limitation in capacity of a normal developmental mechanism which was not geared to handle a large volume of ectopic cells. With a better understanding of the normal monitoring of tissue compartmentalization under the direction of the "immune response," techniques to expand this developmental mechanism are very likely to be therapeutically exploitable with a large volume of ectopic tissue.

The current techniques for managing cancer include mutilation, deadly rays, and lethal poisons. These modern counterparts of trephining out evil spirits can only be thought of as temporizing measures. Diseases of fundamental biology must eventually be approached with fundamental biologic therapeutics. Learning to exploit the best nature has to offer is the best chance to make doctors more sophisticated than the diseases we treat, and will be essential for the much needed improvement in therapeutic ratios of cancer therapies.

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